Combined heart and liver transplantation for familial amyloidotic polyneuropathy

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Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant inherited form of amyloidosis associated with a mutant form of a protein called transthyretin. The abnormal protein results from a single point mutation in the gene encoding transthyretin (18q). More than 70 mutations have been described, the most common of which is Met30 (Portuguese variant), which usually presents as a rapidly progressive autonomic neuropathy in the second and third decades of life. This genotype is not associated with cardiomyopathy, and it is cured by means of liver transplantation alone. The second most prevalent is the mutation Tyr 77 (German variant), which is typically associated with rapidly progressive autonomic neuropathy and cardiomyopathy in the fifth or sixth decades of life, leading to death within 5 to 10 years. Combined heart and liver transplantation is indicated when both organs are involved by the same pathologic process because one organ causes damage to the other organ. Although isolated liver transplantation halts the progression of the autonomic neuropathy, cardiomyopathy usually worsens after transplantation because the transthyretin synthesized by the donor liver continues to precipitate on the abnormal transthyretin already deposited in the myocardium.[1] On the other hand, if cardiac transplantation alone is performed, the patient does not recover because the liver continues to produce the mutated protein.[2] Therefore the therapy of choice is transplantation of the injured organ (the heart) and the organ that produces the injury (the liver).

Materials and Methods

PATIENT 1. A 60-year old man underwent stress test electrocardiography to assess his fitness for sport, but during the test, atrial fibrillation arose. The cardiologist performed echocardiography, which revealed the increased thickness of the walls of the ventricles, small ventricular chambers, dilated atria, and thickening of the interatrial septum, demonstrating also a granular sparkling texture. Six months later, the patient was admitted to the hospital because of cardiac failure, diarrhea, and nocturnal paresthesia. The electromiography revealed the denervation of the anterior tibial muscle and a lower speed of conduction in the left sural muscle. The patient was transplanted 18 months after onset of the disease.

PATIENT 2. A 45-year old man complained of a 2-year history of easy fatigability on prolonged walking. The clinical history could be traced back to when the patient was 43 years old. At that time, he had already noticed constipation alternating with diarrhea and occasional lipothymias. Echocardiography demonstrated a typical speckling pattern consistent with amyloid deposition within the myocardium, and this was confirmed by means of subsequent endomyocardial biopsy. An abdominal fat biopsy also suggested systemic amyloidosis. Abnormal transthyretin protein was detected in the serum, which is consistent with the diagnosis of FAP. The patient underwent transplantation 2 years after the onset of symptoms.

PATIENT 3. A 50-year-old man presented with a 4-year history of asthenia and reduced pinprick and light-touch sensation in both feet. Nerve conduction studies revealed an early sensorimotor peripheral neuropathy consistent with amyloid neuropathy. Echocardiography demonstrated a typical pattern consistent with amyloid deposition within the myocardium, and this was confirmed by means of subsequent endomyocardial biopsy. Abnormal transthyretin protein was detected in the serum, which is consistent with the diagnosis of amyloid polyneuropathy. The patient underwent transplantation 5 years after the onset of the first symptoms.

DNA study on the white blood cells of the 3 patient revealed the Glu 89 mutation.

Operative Technique

The hepatic and cardiac steps of the operation were done by the respective surgical teams. The first step of the operation was the implantation of the heart of the donor into the recipient. After the heart transplantation was complete, the chest was left open and covered with a sterile drape (Steri-Drape; 3M Company, St Paul, Minn). The second step was the liver implantation. After all hepatic vascular anastomoses had been completed, the cardiac team returned to control residual bleeding in the chest, and all incisions were closed.

Postoperative Course

PATIENT 1. The course was good from the first postoperative hours. The patient was discharged from the intensive care unit on the fifth postoperative day. At the seventh postoperative day, a rejection of the cardiac graft was diagnosed by means of an endomyocardial biopsy (grade 3A), and the hepatic biopsy also confirmed liver rejection (grade 2) after an increase in serum transaminase levels. Therefore, corticosteroids (500 mg × 3/day) were used as antirejection therapy, and the subsequent liver and cardiac biopsies demonstrated a frank regression of the rejection. The patient was

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TABLE 1. Previous experiences

City	Hospital	Mutation	In-hospital death	Actuarial survival
Pittsburgh	Presbyterian University Hospital	ALA 60	No	Yes
London	King's College Hospital	TYR 77	No	No (3 y later)
Mainz	Der Johannes Gutenberg Universität	LEU 33	No	Yes
Auckland	Green Lane Hospital	TYR 77	No	Yes

discharged on postoperative day 22 in very good condition. Currently, the patient is well and working full time. His liver chemistry test results are within normal limits, and the endomyocardial biopsy revealed no evidence of rejection or amyloid deposits.

PATIENT 2. The operative course of this patient was complicated by bowel ischemia (caused by a venous thrombosis), for which he was treated with a right hemicolectomy and ileostomy at the end of the transplantation. The patient was discharged from the intensive care unit on postoperative day 13 with good heart and liver function. The postoperative course of this patient was complicated by malabsorption syndrome until the intestinal continuity was restored. He was discharged from the hospital on postoperative day 120. The patient's liver chemistry test results were normal, and the echocardiogram showed a very good cardiac performance. Currently, he has normal liver function, and the endomyocardial biopsy revealed no evidence of rejection or amyloid deposits.

PATIENT 3. The postoperative course of this patient was characterized by a re-exploration for bleeding. An endomyocardial biopsy revealed a grade 1B rejection on postoperative day 18 that was immediately treated with antithymocyte globulins. Liver chemistry test results were within normal limits, but from postoperative day 3, the patient became anuric with high levels of creatinine (8 mg/dL), and therefore he underwent dialysis every other day. The pharyngeal tampon was positive for *Candida albicans*, and *Aspergillus fumigatus* and *Pseudomonas aeruginosa* were identified in the bronchial aspirate. Chemotherapy was started, but the patient died on postoperative day 60 as a result of septic shock.

Discussion

Including our 3 patients, there are 7 patients worldwide who underwent combined heart and liver transplantation because of FAP (Table 1). The patients presented the pattern of restrictive cardiomyopathy.

Although disease progression is halted with liver transplantation alone, it has been suggested that progression of FAP is possible after transplantation. Dubrey and colleagues[3] recently reported that some patients with FAP showed continuous left ventricular wall thickening after liver transplantation, with a concomitant trend toward deterioration of ventricular function. This study also showed that ventricular wall thickening was more frequent in patients with FAP who had undergone transplantation and who had non-Met-30 transthyretin mutations.

Similarly, Pomfret and coworkers[4] recently showed that those patients with echocardiographic evidence of ventricular wall thickening before liver transplantation progressed postoperatively despite neurologic improvement. Dubrey and colleagues[3] suggested that amyloid fibrils already present, for instance, in the heart of the transplant recipient could act as a nidus for nonhepatic sources of mutant transthyretin or for the deposition of normal transthyretin produced by the transplanted liver. Although there is concern that amyloidosis is a systemic disease that might result in both recurrence in the donor heart and progression of the disease in other organs, the extremely poor prognosis of these patients raised the possibility of heart transplantation as a potential therapeutic procedure. However, a later multicenter survey suggested that initial enthusiasm was premature because the patients had restrictive cardiomyopathy.[5]

Actually, 5 of the 7 patients who underwent heart and liver transplantation are alive. There was not a progression or recurrence of the disease with standard immunosuppressive therapy, and these patients have a very good quality of life. Therefore, according to our experience and literature data, we believe that combined heart and liver transplantation should be considered an efficacious therapeutic option for patients with FAP.

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